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10/511,822	03/23/2005	Aurelio Orjales Venero	P/4043-153	6533

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EXAMINER	
CHANG, CELIA C	
ART UNIT	PAPER NUMBER
1625	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,822	ORJALES VENERO ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The previous office action is hereby replaced by the instant office action based on a preliminary amendment filed on April 11, 2005. The time of response has been reset with respect to the mailing of this office action.

Claims 1-24 are pending.

2. Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "polymorph 1" in claims 1-18 are ambiguous and indefinite. Please note that the term "polymorph" is referring to multiple crystalline forms. It is unclear are the claims being drawn to bilastin crystalline form I or are the claims being drawn to *polymorphic forms of form 1* which means not form 1. If the claims are drawn to a single crystalline form 1, then, the term polymorph should be deleted.

The term "at least one of isopropylic alcohol and n-butanol" in claims 19-24 is confusing and may be broadening of the base claim. Please note, at least one includes other solvent which is not encompassed by the base claim. In addition, "at least one....and..." is confusing, is it propanol **or** butanol? or at least one mixture ? or a mixture containing one of the alcohol? Clarification is required.

The term "preparing a medicinal product for treating allergic reactions and pathological processes mediated by histamine" is very confusing. Is this a process of making a medicinal composition? Please note that there is no steps in the claims since "incorporating" is not a step and criticality of how such process is conducted must be explicitly stated. Further, it is unclear what was made? A therapeutically effective amount? An antihistamic effective amount? Please note that a process "mediated by...." includes both too much and too little. An antihistamic compound can only treating too much histamine. In addition, for a pharmaceutical composition, the active ingredients are normally mixed with pharmaceutically acceptable carriers which constitutes a composition. Clarification is required.

3. Claims 1-3, 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A product cannot be separated from *all* its physical properties. Applicants have not demonstrated that a product with X-ray analysis alone without the IR spectrum nor vice versa.

4. Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to "procedure" consisting of one step, i.e. heating in a solvent. Please note that a procedure must contain steps of how the process is being operated. Absent of starting material, conditions such as temperature, concentration, for how long, and separation, the claims are inoperable. Heating alone does not obtain the claimed product.

5. Claims 4-5, 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with - which it is most nearly connected, to make and/or use the invention.

"The standard for determining whether the specification meets the enablement requirement [in accordance with the statute] was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v. Telectronics, Inc.*, 857 F.2d 778,

785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.").

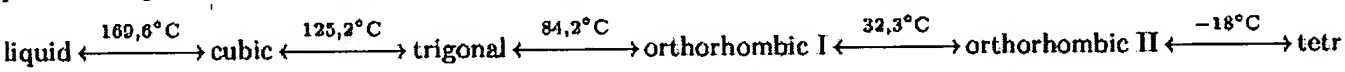
In the instant case, the rejected claims 4-5, 15-18 which were not described in the specification. Based on the level of skill as stated in the state of the art reference *Kirk-Othmer Encyclopedia of Chemical Technology* Copyright © 2002 by John Wiley & Sons, Inc., pp. 95-147, Article Online Posting Date: August 16, 2002, the amount of guidance in the specification, the disclosure does not contain sufficient information to enable one skilled in the pertinent art for recovery of such a product as claimed.

Specifically, the amount of guidance or direction needed to enable an invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof."

In the instant case, the state of the art of polymorph recovery is highly unpredictable. See for example *Kirk-Othmer Encyclopedia of Chemical Technology* Copyright © 2002 by John Wiley & Sons, Inc., pp. 95-147, Article Online Posting Date: August 16, 2002. This article

indicates that many uncertain factors determine morphology, and specifically that the appearance of the crystalline product and its processing characteristics (such as washing and filtration) are affected by crystal habit (i.e., the general shape of a crystal). Relative growth rates of the faces of a crystal determine its shape. Faster growing faces become smaller than slower growing faces and, in the extreme case, may disappear from the crystal altogether. Growth rates depend on the presence of impurities, rates of cooling, temperature, solvent, mixing, and supersaturation. Furthermore, the importance of each of these factors may vary from one crystal face to another, see page 114.

The reference also teaches that polymorphism is a condition wherein crystalline form is intimately associated with processing ("*Polymorphism* is a condition in which chemically identical substances may crystallize into different forms. Each form is, however, only stable (thermodynamically) in a certain range of temperature and pressure. In the case of ambient pressure, eg, ammonium nitrate exhibits four changes in form between -18 and 125°C:



Transitions from one polymorphic form to another may be accompanied by changes in process conditions (temperature, pressure, shear or solution composition), transitions from one polymorphic form to another and lead to formation of a solid product with unacceptable properties (eg, melting point or dissolution rate).

Critical elements such as temperature, time, concentration, kind and ratio of mixture of solvents etc. must be explicitly limited for any procedure to produce the particular crystal as claimed. Especially, it is unclear whether the claims are making form 1 bilastin or "polymorph" of bilastin form 1.

6. Claims 9-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270

(1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

The analysis is applied to the instant case.

Nature of invention

The claim is drawn to a composition having the particular "Form I" of bilastin.

The state of the art and predictability

Per ponderous of factual evidence in "drugs" indicated that the temperature and pressure of pharmaceutical composition processing *would* cause transformation of "forms".
See :

Muzaffar et al. p.60 "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form ...." And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;

Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

Doelker et al. abstract, "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or the dosage form"

Doelker et al. abstract "...a given drug, although chem. well defined, may exhibits quite different behavior. Process conditions (*grinding, tableting, granulations, drying)* may also affect secondary properties of the drug, such as compactibility, wetttability, soly, dissoln, rate, bioavailability and even pharmacol. activity."

Otsuke et al. p.852 « ...in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic *phase transformation* of the bulk CBZ powder during the manufacturing process"

Taday et al. p.831 « ...Once in the desired crystalline form, the polymorphic state *may be changed* by incorrect storage or even during tablet preparation" and p.836, figure 8, wherein compound of four form in pharmaceutical composition resulted in similar spectra i.e. form.

The amount of guidance and working examples

On pages 8-10, description of pharmaceutical composition using conventional carrier such as water, aqueous solutions etc. were disclosed. In addition, conventional procedure for pharmaceutical formulation including wet processing and dispersion. No where in the specification was a composition of "form I" which is defined explicitly to have all the properties with X-ray, IR etc., that is the composition contain a material that has the same X-ray diffraction pattern essentially as shown on page 2 or IR of figures 1-3. Nowhere in the specification a *composition* of this limitation of the claim was made.

In view of the per ponderous of evidence as delineated supra, it is evidenced that crystalline drug does not *automatically* keeps its form in the pharmaceutical composition, thus, *absent of any description or enablement* from the specification, enablement for the "claimed" composition is lacking.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Orjales et al. Us 5,877,187, see col. 10, claims 8-21, or *alternatively*;

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orjales et al. US 5,877,187, in view of Rowland and Tozer supplemented with Corcostegui et al.

It was evidenced in the conventional teaching in the physiology of the human body that dissolution of the orderly packing i.e. crystal of a drug can occur at several stages of drug

kinetics. The first location is in the formulation stage wherein a liquid dosage such as injection ample, liquid capsule etc. was employed, then the active ingredient i.e. crystal of bilastin is being administered in the dissoluted compound "bilastin". In this scenario, anticipation is found since both the active ingredient and its outcome are identical to the prior art. The polymorphic form, upon formulation into liquid or compression would produce the same identical thermodynamically stable product of the prior art see col. 10, claims 8-21. Therefore, the pharmaceutical composition or method of using of claims 6-10 would have the dosage, site of administration and efficacy being the same as the prior art and anticipation was found.

The other location of dissolution can be expect at either the absorption and distribution stage (see Rowland and Tozer) or at the cellular level wherein the 4-[2-[1-(2- ethoxyethyl)-I H-benzidimazole-2-yl]-1-piperidinyl]ethyl]-aa-dimethyl- benzeno-acetic acid is inhibiting histamine production. Either stage of the claimed process would be a prima facie obvious modification of the prior art process employed by Orjales et al. '187, because one skilled in the pharmaceutical art would be motivated to modify the prior art method for a purer form (see '187 col. 5-6) especially, such modification is routine practice as *evidenced* by the preclinical trial (see Corcostegui et al.) of the drug.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-5, 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orjales et al. US5,877,187 in view of Cheronis.

Determination of the scope and content of the prior art (MPEP §2141.01)

Orjales et al. US 5,877,187 disclosed process of making the compound wherein variation of solvents were included in the process (see col. 7, example 2).

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference of the instant claims and the prior art process is the employment of choices of solvents in a further purification by crystallization. Cheronis taught that purification by crystallization is routine laboratory practice and one skilled in the art is well aware of all the available laboratory solvents and the process of testing and picking a suitable alternatives (see p.31-35).

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art will be motivated to modify the Orjales' process with the known technique of picking and choosing a different solvent system for crystallization, especially, lower alcohol is ordinary laboratory solvent and has been used in analogous compounds (see '187 col. 8, example 4).

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Dec. 18, 2007

Celia Chang
Primary Examiner
Art Unit 1625